DNA: Discoveries in Action Season 4 Episode 3 Transcript

Jeff Balser: It's never been done before. There has never been a whole genome sequencing project in the United States at this scale, and it takes big industry partners to make that happen. So we're really excited about it.

Nancy Jean Cox: So the recent announcement is a very exciting development. I think it reflects the quietly growing, but actually really remarkable, trajectory of Vanderbilt University Medical Center.

Jeff Balser: I think the history of big things getting done are public-private partnerships. I mean, if you go back to the Manhattan Project, it was researchers at universities coming together with the federal government and industry, and it's been that ever since.

Clark Buckner: Welcome back to the fourth season of DNA. I'm so glad you're here. I'm your host, Clark Buckner, and over the next four episodes, we're going to take you on an exploration of how Vanderbilt University Medical Center is tackling the same challenges that companies across the world are. From forging a visionary pathway to the changes in the workforce, this season is a glimpse into how smart people approach problems. We'll see it's not quick, and you have to have confidence in your people and their ideas.

At the top of this episode, you heard from Dr. Jeff Balser, CEO of VUMC, and Dr. Nancy Cox, director of Vanderbilt's Genetic Institute, describing how VUMC recently launched a landmark partnership that will influence the future of genomic research. It will shape our understanding of how DNA interacts with medicine.

It's called the Alliance for Genomic Discovery. And it's an offshoot of VUMC's subsidiary Nashville Biosciences, which was created to interface with outside partners to use the Medical Center’s extensive genomic and bioinformatics expertise to advance drug discovery and development. VUMC and Nashville Biosciences brought in Illumina – a publicly traded company that is a global leader in DNA sequencing and array-based technologies – to expand the potential reach. It's a fascinating exhibit of how big things get done.

Illumina, Nashville Biosciences and VUMC partnered with FIVE global pharmaceutical companies. The alliance with AbbVie, Amgen, AstraZeneca, Bayer, and Merck will co-fund the whole genome sequencing of 250,000 DNA samples and will use the resulting data for drug discovery and therapeutic development.

This alliance didn't happen overnight, it's the culmination of decades of ingenuity and creativity across Vanderbilt's clinical and research enterprise. People were thinking and building for the future of technology before it even existed. They had support from people who took the long view, including Dr. Balser, who bought into the vision more than 30 years ago. Let's hear his take on how a futuristic proposal became a groundbreaking reality.

Jeff Balser: I kind of think of the future of the Medical Center holistically, but with kind of highways that are converging on one another. And one of the highways has to do with the hardcore biological science that we do. And that makes me think of the recent announcement around the Alliance for Genomic Discovery, which interestingly– and I call them highways that are intersecting. If we weren't a huge healthcare system that wouldn't exist because BioVU is the largest single-site DNA repository in the country. And what BioVU is, is 300,000 DNA samples linked to deep, rich longitudinal health records from 300,000 patients. So if we hadn't been an academic medical center that is a health system with its own health record collecting DNA from patients who are our patients for lengthy periods of time, this DNA repository wouldn't be worth anything.

The real value of BioVU is what's in the patient information. Because if you really think about it, DNA on its own is useless, the value of DNA comes when you actually associate it with something. And the health record, especially a longitudinal health record with our patients being on average 10 years in the system, is like a Rosetta Stone for DNA, and we have the largest, most complete, and comprehensive Rosetta Stone on the planet linked to our health record. So telling people that is one thing, but having them really understand it is another thing. And by the way, I have to say that the reason this all works is that health record is de-identified before it's married to the DNA. So the patients are entirely protected because they're avatars. You don't really know who the patients are, but the disease information is all there, and that's linked to the DNA. And so we start to get an understanding of, in 300,000 people, if you have this DNA variation and then you have these diseases, drug side effects, all kinds of stuff.

And the other thing that's different about BioVU is that it's a movie, not a photograph. So there are large DNA repositories all over the world. The British Biobank is one of the more famous ones. It's linked to a snapshot of about 50 different health records from places all over the UK. And the snapshot is at the moment in time the DNA is taken, right? So whereas what we have is a continuous movie of health activity that goes on forever and ever as long as the patient's getting their care at Vanderbilt.

Nancy Jean Cox: So the biobank was originally conceived by Dan Roden here at Vanderbilt, who's a cardiologist interested in cardiac arrhythmias that often arise as a consequence of some sort of drug interaction. Certain drugs that people take can induce these cardiac arrhythmias. And so that's a kind of pharmacogenomics. It was clear to him that to really develop all of the samples that you needed to understand, to find the genetic risk factors for this, to really understand what was going on in these people, you'd have to be able to collect almost everyone taking any of these drugs. And as it happened, Vanderbilt invested in development of their own electronic health records now more than 30 years ago.

And the concept of a biobank linked to electronic health records as the way to understand all of the diseases that people have, what their trajectories in that disease space are, it was clearly a major brainstorm to envision how, because of the long history of electronic health records data

collection, the possibility of creating a biobank from leftover blood samples. When people get a clinical blood draw ordered after about three days, when it's clear they won't need any more of that sample for any more tests, they generally just throw the blood away. And so they worked out a system where, for patients who consented, the leftover blood could be used to extract DNA and then that DNA stored and linked to all of these electronic health records. So that immediately creates a huge opportunity for genetically-based research.

You have sometimes 10 to 15 years on average of electronic health records data on subjects. And then it was set up from the beginning so that, if you could do some genetic interrogation in a set of samples – for example, the people who develop arrhythmias after taking a drug – you would deposit that data back into the system so that other people could do research investigations with that same data. And that just creates a virtuous cycle of more and more genomic data accumulating on these subjects, that more and more people studying different diseases, different even longevity, and good health over the lifespan could really use in genetic studies without having to collect brand new samples. It became much less just a DNA repository and more of a really big data engine, basically, for research and discovery.

Jeff Balser: It's going to take two years to hold genome sequence, the entire bank. It's going to happen in Iceland. And it's just a monstrous project, but its manifestations are mind-boggling. In terms of the kind of information in large scale, we're going to have to discover new drug targets, to understand drug side effects, to think about all kinds of disease trends and predictors of disease that we just haven't been able to get out of the 1% of the DNA sequence we've had, which is the exome. Now we'll have the 99%, which is all the things that regulate whether you make more or less protein, not just whether you have that protein.

And if you think about the way medicine has been designed over the last few hundred years, it's based on clinical trials of different things that look at hundreds or thousands of patients, and we take the average result and then we design care around the average. Well, that was the best we could do, and it made sense. It's not going to make sense anymore. What the average response to this drug is no longer going to be even relevant to your care because you have this DNA profile and this is how you will respond to this drug. And oh, by the way, your dose is 10 times greater than anybody else's that you know, that's where we're going. Yeah.

It's already happening. I mean, there was a huge lawsuit in the state of Hawaii in the last few years based on Plavix, which is– You'll recall one of the first drugs that Vanderbilt rolled out in its PREDICT program where we basically are genotyping patients at a certain set of genes that predict whether or not Plavix will be effective as an anticoagulant.

So patients have coronary artery disease and they have a stent placed in their coronary artery, those little bridges they can put in in the cath lab. And after patients have that done, they have to be anticoagulated for a while, and the drug most often used is Plavix. And it's very effective except when it's not. And if you're 1 or 2% of people that has a DNA variant, which is the rate at which that happens in Caucasians in the United States, you go home thinking you're on Plavix,

but you're really on a water pill because the Plavix isn't metabolized. Well, what happens if instead of American white people, it's Hawaiian Islanders? Turns out it's double-digit percentages in that race. Well, lots and lots of people were going home after their stents in having heart attacks, and they sued as a class action and won, and the settlement was close to a billion dollars. It's the first time that any of us know of there's ever been a major legal case that was a pharmacogenomics case because that was knowable ahead of time.

Clark Buckner: So we've heard about how researchers are drawing up the blueprint for the future, but what does this mean for us? How could we experience and benefit from a smarter medicine?

Nancy Jean Cox: So the stuttering project that Jennifer or Piper Below led from our Division of Genetic Medicine in the VGI is a particularly interesting example of a study in the biobank that required some really thoughtful applications of big data science. So because stuttering is not really a medical condition, it's often not cataloged among the health problems that people have. Even people who get therapy for stuttering, it's not usually in the context of a medical setting, it's speech and language pathologists who do that. But we had many people with enough information about being stutterers in the physician notes that they could identify a set of gold standard diagnosed stutterers and then learn the medical phenome that was associated with stuttering in those people and using machine learning techniques, develop a predictive model of other medical phenome so strongly associated with stuttering that it captures a good portion of the genetic liability.

And they were able to collaborate with 23andMe to get data on about a million people who had self-reported information on whether or not they stuttered. And so they were able to show that their machine learning approach to this diagnosis developed in our biobank corroborated the genetic liability that was identified through the very large-scale data in collaboration with 23andMe. So it's a beautiful example of how modern big data science tools can be used to help us to study even diseases that are not routinely collected as part of general medical care. Yeah, so one of the main reasons that we do genetic studies for diseases that we know have some contribution of genetics, and for example, the heritability of stuttering is quite high, so that we know that genetic factors influence the probability that people develop stuttering in the first place and almost certainly also determine the likelihood that they will recover spontaneously. I mean one of the key reasons that we do genetic studies is that we expect these to give us insights into the underlying biology of conditions that we don't fully understand. To be perfectly frank, there are very few medical conditions that we completely understand. We understand enough to treat many things but understand poorly enough of the causes. We don't even have biomarkers for many diseases, and we certainly don't have good therapies for a lot of conditions that we wish we did.

By using the genetics to understand more of the driving biology, we put ourselves in a better position to do rational drug design to target the actual biology that drives these conditions. And stuttering is a great example of one that I think anyone who's ever worked with stutterers, who

has ever stuttered themselves, knows how valuable it would be to be able to take a pill and be fluent for some period of time where you felt like you needed to be fluent. And there are many medical conditions that we do believe that, if we could understand the biology better, we might recognize more clearly also the non-genetic determinants of health that can be modified to reduce risk, maybe even to prevent disease.

Bill Stead, who was head of our strategic initiatives for many years here at Vanderbilt and before that ran the Department of Biomedical Informatics and was hugely instrumental in building out the electronic health records here, was so compelling with his vision of why we need to have electronic health records. He would say, "A doctor's diagnosis is not truth, it's data. A test result is not truth, it's data." It's all just data to compute over to learn more about truth, which is what we have to have in medicine and in drug development. We want to have improved standing that allows us to drive the whole set of health machinery forward – better drugs, better diagnosis, clearer pictures of what different people's trajectories are likely to be, and where our best intervention points are.

I think this partnership really should be just the beginning of new kinds of ways that we interact with the kinds of industries that are most interested in the kinds of research that we do here, and in the unique confluence of expertise in electronic health records development and research, the biobank and the huge amount of genetic data we have and will now continue to enrich.

Clark Buckner: By now, I think it's quite possible you've heard about ChatGPT, but that's a generative artificial intelligence. AI is actually already embedded in our life and healthcare, but what's new now is that the public has access to these tools. Medicine and research, on the other hand, have been using and building on AI for decades. We're entering an era of technology warp speed. It's exactly what is predicted in Moore's Law. Dr. Peter Embi leads Vanderbilt's formidable biomedical informatics program. Dr. Embi is a renowned expert on AI and is part of the NASEM steering committee on generative AI. He's excited about the opportunity ahead.

Peter Embi: The ability for tools like this to actually be able to help us accelerate the diagnostic odyssey that a patient is on and shorten the time to actually getting a diagnosis and therefore being able to treat them properly is something that we can make real today. So a lot of what we do in research, overall, is inherently risky in the sense that we don't necessarily know what's going to work. We don't necessarily know whether a particular experiment is going to work. In fact, if we did, we wouldn't do the science. So there is a lot of that. That's sort of inherent in what we do.

But we always do it, particularly in the area that I work in – in biomedical and health informatic – we always do it with a focus on having an impact on solving a real-world problem in the healthcare environment or in the biomedical environment, whether it's discovering some new way of diagnosing and treating people or whether it's figuring out how to better take care of people and populations. And so, in that regard, while we're doing a lot of things that maybe

aren't quite ready, once we determine that they work and that they're actually functional and they're going to help, we don't want to be accused of having a failure of imagination.

Clark Buckner: I've played around quite a bit with tools like ChatGPT and AI-generated art tools like Midjourney. It will come as no surprise that the bias that underpins our society emerges instantly in the outputs of these models. That's because they're trained on what already exists and what exists is biased. That's problematic for people who are striving to make healthcare and medicine equitable for all. Dr. Embi, himself, has spent years researching vigilance and ethics in AI algorithms. He has even coined a phrase algorith-ma-vigilance.

Peter Embi: What we know is that we train these models, we train these algorithms using the data we have, and the data we have come from the environments we have, which include inherent biases. And we know that they inherit the biases of our society because there are people who have more access to care than others. And we know that there's a disparity there, and we know that, therefore, the data that we're using to train these models is inherently going to have some biases. We have to take those into account because then when we go ahead and deploy these, if we're not paying attention to that, we can have unintended effects on populations that aren't as well represented in the data, and yet we're taking care of. So for instance, Black populations or Hispanic populations may not be as well represented in the data as some of our white populations. Well, there could be inherent differences there.

So we know about some of those and we take those into account. But, importantly, there's also the issues that come up that we simply can't anticipate. So one of the things that we've been thinking a lot about, and that I've been really writing about for some time, is this concept of needing to be vigilant when we deploy these algorithms in practice. That we monitor them to make sure that not only they're having the beneficial effects we expect, but that they also aren't having adverse effects, that they're not actually harming. And we take a principle from the pharmaceutical industry.

So when a drug gets approved by the FDA, it's usually been through studies with maybe thousands of people, and then we deploy that into the world and people start to use the drug, and now it's being used by millions of people. And, oftentimes, in those situations, we find side effects, adverse effects, that we weren't anticipating. And that sort of the science and the approach of how you monitor for that is called pharmacovigilance. So pharmacovigilance is this concept of monitoring drugs when we put them out into the market to make sure that they aren't having unintended adverse effects on populations. So we develop algorithms from these activities and we want to be vigilant about monitoring them.

And again, the whole intention of that is to say, how do we systematically monitor for these, so that– We do a few things, one is we make sure we're not causing harm, and if we are, we can address it. But also we want to do it because we want to create the safest, most effective environment possible, and we want the system and everybody in it to trust that these are actually good because we know that algorithms can help us. We know that the way we're

practicing medicine right now can be improved. It's not nearly as good as it needs to be, and we have to do a better job of actually using these tools and these data to make better decisions. But if we aren't vigilant about, not only the things we anticipate might go wrong, but especially those things that we can't, then we're not going to know and we could harm people. So that's a big part of what we're focused on.

Clark Buckner: It is fascinating how the research industry can carve this path forward amid astonishing changes in technology and society. While these ideas have sprung out of a campus in Nashville, we're going to hear from the chief of the Vanderbilt Institute for Global Health about the necessity of harnessing ideas and expertise to improve health equity around the world for everybody. Dr. Muktar Aliyu is an expert on translating best practices from one medical culture to another. Let's hear from Dr. Aliyu about how technology and AI is being used in other countries.

Muktar Aliyu: So if you look at countries like Nigeria, half of the population is younger than 18. Half of the population, they're 18 years and younger. So if you think about artificial intelligence, you think about digital health, when you think about all these innovative technologies that are coming in, telehealth, our ability to do gene editing and edit out genes that are responsible for transmitting malaria and mosquitoes. All these high-tech innovations are things that come relatively more easily to younger people than they do to some of us who are older. And those are the things that are going to drive innovations in global health in the coming years.

Some of our countries that have aging populations, the other thing would be priorities. We have to shift some of our priorities away from, let's say, acute care to how do we provide long-term care to these populations, how do we improve the quality of our geriatric care services. Even the nursing shortages, they're partly driven by demographic changes. Countries like Japan, if they're not facing challenges like that, they soon will because young nurses are what you need to prime the pool. And if you don't have young people, then you don't have that pool from which young nurses would be drawn from.

Non-communicable diseases. There are a lot of non-communicable diseases that are more prevalent as people get older. So we are going to see more cases of diabetes, more cases of hypertension and stroke, and heart disease just because those conditions are more common in older people. So we have to put in place systems that will be able to provide good quality care, rehab services. Even cancers, a lot of cancers are age-related. So those are some of the things that we'll have to work collectively to develop innovative solutions for, and at the same time, do adequate planning for when those needs will arise.

Global health is about addressing disparities between populations, which we know we have a lot of here. Global health is about looking at solutions that are simple, practical, and can be sustained. Global health is about using technologies that are not necessarily high-tech, high-end technologies, but really technologies that have been shown to work in other settings and that are cost-effective, and they can be easily adapted to specific populations. So it's not about work

outside of the US, we're all part of the globe. It's about one– There's a concept of one health where you look at both human health, animal health, and the environment. The world is shrinking every passing year. Borders are no longer a major issue these days. So being able to collectively work together, whether it's a developing country or a developed country setting, and provide care for our populations, that's what global health is about.

So we talk about personalized medicine, where we are able to actually target– Someone has a specific disease condition, we're able to do some testing and say, "Okay, this is the drug that would work best, or this is the best way to approach our treatment in this particular patient." Now, if we have a scenario whereby most of the people that we recruit into our clinical trials are, that it's not a diverse population, then essentially what happens then is the benefits that accrue from the findings of those clinical trials would not extend to those minority groups. And the advantage we have is Sub-Saharan Africa. Africa has the widest genetic diversity. That's where we all originated from. So having samples, especially being able to include people of African ancestry into these clinical trials, especially genomics-related studies, is extraordinarily important in terms of equity and being able to provide benefit that accrues to all people.

So because of that, or partly because of that, we've had a lot of interest from faculty members here at VUMC who do genomics, omics related research. We've had people like Digna Velez Edwards, who's in the Department of Obstetrics and Gynecology. She's looking at genomics of uterine fibroids, which is a disease condition that's very common in Black women. And obviously, for studies like that, you do need a large sample of minority populations. We have people like Ed Trevathan who's looking at the genomics of childhood status epilepticus, a very severe form of epilepsy. There is some evidence coming from mostly predominantly white populations, so now he's working on getting a larger sample from Nigeria. Same thing with our sickle cell disease work. We're working on preeclampsia with Sarah Osmundson and Kate Lindley in Cardiology, Women's Health Center. So there are opportunities, definitely, there are opportunities there that we can use our collaborators in those settings to design really well-designed clinical trials or genomic studies that would help contribute data from those specific populations.

The thing is with global health, we've seen that disease conditions just do not respect national borders. You can have someone with Zika or Ebola get on a flight and within a couple of hours, they're here in the US. So these are issues that directly impact the healthcare of citizens living here in the United States. We can learn from global health lessons. We have several countries that have shown us that we can provide high-quality healthcare at a much lower cost than what we are currently doing. In fact, the United States, if you look at the health indices, a lot of our health outcomes are nowhere close to the health outcomes that we get in other countries that are less endowed in terms of wealth, the national wealth.

You look at our life expectancy, the life expectancy of an American that's born today is almost a decade less than the life expectancy of someone born in Japan. We look at death rates for some of the non-communicable diseases, diabetes, and hypertension, adverse outcomes

associated with those conditions are much worse in the US than they are elsewhere.

And even more importantly, disparities. We have major disparities across populations here in the US. And we can learn, we can learn from our global health experiences. We can innovate. We can develop innovative solutions, adapt them to our own circumstances, learn from things like community engagement, things like task shifting, training people like nurses and community health workers to provide services in places where physicians are not available. So there are major important lessons that we can learn from global health and adapt to our own system here.

Clark Buckner: In fact, diversity is so critical in understanding different populations that the first 35,000 DNA samples to be sequenced will be from African Americans. The Alliance is rooted in Nashville but is a very global project that's being sequenced in Iceland and will absolutely reverberate in communities around the world. The seeds of the Alliance were planted nearly 40 years ago when Vanderbilt developed its own EHR system. It's taken years of investment and constant nurturing, yet this is the story of how a few people looked into their crystal ball and saw how technology would pave the road to a smarter and more person-centered future in medicine.

Jeff Balser: We joke about after the press release, "Does anybody realize how many Friday afternoon phone calls we had to get to the Alliance for Genomic Discovery?" We were going back in our calendars. It's like, we had a Friday afternoon phone call, virtually weekly, for three years just to deal with all the kind of administrative, governance, security, financial types of issues we had to get our heads around in order to make that happen, let alone the science, which goes back to the health record at Vanderbilt being digitized in 1995, 10 to 15 years before anyone else.

So the things that lead up to something like that go back decades really. When the Alliance for Genomic Discovery was announced and the press releases came out, and there was an email that came out with the press releases from Leeland Ekstrom, who leads Nashville Biosciences, and he copied a lot of people, some of whom were members of the advisory board for the company, and one of those individuals was Dan Roden. And Dan was one of the founders. There were two founders who together created BioVU back in the early 2000s, Dan Roden and Dan Masys, who was head of biomedical informatics here and was the former founder of the National Center for Biocomputing at NIH. And the two of them, we called them the Dans in those days when we were creating BioVU. I was head of research then, so I was trying to put all the pieces together to help them do what we knew was just a remarkable innovation.

That was the early 2000s, it seems like forever. I mean, I wasn't even in the job I have now then. So I couldn't resist calling Dan. I just called him on his cell phone and he picked it up and he knew it was me, and he said, "What do you want?" And I said, "So Dan, this idea of connecting DNA to the health record might've been a good one." And he just laughed. He said, "I think we did a good thing." But it's like one of those moments where it all made sense. It's a 40-year story.

Clark Buckner: It's great to be back for season four. This time around, we're taking a new approach, a four-episode case study about how an academic medical center in Nashville is looking at re-skilling a workforce, how they're developing education and training pathways and pipelines into nursing, and how kernels of an idea can lay the groundwork for bold change. We'll be hosting some live chats this fall. Be sure to find Vanderbilt Health DNA on LinkedIn to be part of the conversation. We're looking forward to seeing you there.

To hear more from Dr. Nancy Cox and learn about the progress of the Alliance, visit listendna.com. Until next time, Vanderbilt Health Making Health Care Personal.
As a reminder, Vanderbilt Health DNA: Discoveries in Action isn't meant to replace any form of medical advice or treatment. If you have questions about your medical care, consult a care provider.